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A technical note concerning non-adherence to drug therapy: exact expressions for the mean and variance of drug concentration

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Abstract There is considerable evidence that prescribed drugs are not taken as intended. We present a stochastic pharmacokinetic mathematical model that can be used to assess the implications of non-adherence to prescribed drug regimens, on the part of either patients or health professionals. In the context of an orally administered drug, explicit equations are derived for the time varying mean and variance of the concentration of the drug in the serum, depending on the probability of each scheduled administration being omitted. The analysis presented here can be used to assess whether a given level of non-adherence is likely to have a clinical impact. The methods used can easily be adapted for use in the context of other routes of drug administration.

Keywords Pharmacy · Pharmacokinetics · Non-adherence · Mathematical modelling · Stochastic analysis · Compartmental models

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1 Introduction

For medicines to work as intended, they should be taken as prescribed, yet there is considerable evidence that this frequently does not happen. In-hospital studies have shown that drug administration errors are relatively common, with 3–8% of non-intravenous drug administrations involving at least one error, omission of the administration accounting for roughly half of this figure [1–8].

Outside hospital, non-adherence is also a major problem. Many studies [9–11] have shown that frequently patients do not take their medicine as intended. Adherence to a drug regimen is particularly poor for those with chronic conditions [11], with only around 50% of patients taking their medicine as prescribed [10]. The adverse effects of not taking medicine as prescribed have been observed in empirical studies [12–14]. Within this literature, the focus tends to be on the important question of quantifying patient adherence.

To date, little attention has been paid to the question of modelling the harm associated with non-adherence (either on the part of the patient or due to an error by a health care professional in the prescribing, dispensing or administration of the drug). In this paper, we discuss mathematical modelling methods that can be used to explore this in terms of consequent pharmacokinetic effects. Others have investigated the same topic using computer simulation [15, 16]. However, the analysis presented here is purely mathematical, showing that in some circumstances it is possible to derive explicit stochastic pharmacokinetic formulae for the time varying mean and variance of the serum concentration of a prescribed drug.

Our analysis gives a powerful extension to existing pharmacokinetic theory and, while discussed here in the context of a simple first order absorption and elimination

system, it has much wider applicability. One use of our analysis which we discuss concerns assessing how non-adherence can disrupt one of the main clinical aims of drug therapy, that of achieving drug concentrations that fall within a given therapeutic range.

2 An elementary pharmacokinetic model

Pharmacokinetics is one of the most common uses of mathematical modelling within health care. Compartmental models are used to describe the absorption, transport and elimination of an administered drug by the body. A simplistic view of such models is that each compartment represents a physiological entity within the body, such as the gut or the serum. In practice pharmacokinetic modelling can be more general, compartments often not being explicitly identified with physical subsystems of the body. However in this paper we adopt the former view, extension to the more general case being straightforward. The quantities of drug present in each compartment are modelled as being governed by a set of differential equations, solutions to which can be used to derive time-varying expressions for the quantity of drug present, given a specific drug regimen. Such analysis will be illustrated with a simple pharmacokinetic model reflecting the effects of oral administration of a drug (see Fig. 1).

We first introduce notation, denoting the quantity of drug in the gut at time t by $Q_1(t)$ and the quantity of drug in the serum by $Q_2(t)$. We assume that the serum has an apparent volume of distribution of V, thus the concentration of the drug in the serum is $Q_2(t)/V$. The rate parameters α_1 and α_2 respectively reflect the rate of transfer of the drug from the gut to the serum and the rate of elimination of the drug from the serum. In this example they are assumed to have different values.

We assume that drug absorption and elimination are first order processes, such that $Q_1(t)$ and $Q_2(t)$ are governed by the following system of differential equations:

$$\frac{dQ_1(t)}{dt} = -\alpha_1 Q_1(t) \tag{1}$$

$$\frac{dQ_2(t)}{dt} = \alpha_1 Q_1(t) - \alpha_2 Q_2(t) \tag{2}$$

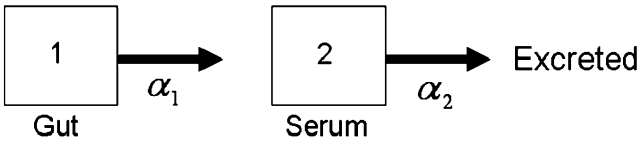

Fig. 1 The compartmental representation of the pharmacokinetic process associated with oral administration of a drug

If the drug is not administered between time t_0 and some later time $t_0+\tau$ then solutions to Eqs. 1 and 2 are given by:

$$Q_1(t_0+\tau) = Q_1(t_0)e^{-\alpha_1\tau}; \tag{3}$$

and

$$Q_2(t_0+\tau) = \frac{\alpha_1}{(\alpha_2-\alpha_1)}(e^{-\alpha_1\tau} - e^{-\alpha_2\tau})Q_1(t_0) + Q_2(t_0)e^{-\alpha_2\tau}. \tag{4}$$

3 Modelling the effects of a sequence of drug administrations

We now consider a sequence of oral drug administrations. As is standard within pharmacokinetics, the effects of such a regimen is modelled by assuming that $Q_1(t)$, the quantity of drug in the gut, increases instantaneously by the size of each dose administered at the scheduled time for administration (for instance see [18]). This implicitly assumes that an administered drug is completely absorbed, however the adjustment to the analysis required to take account of incomplete absorption is mathematically trivial.

Introducing additional notation, suppose that there is a schedule of drug administrations of doses $\{d_0, d_1,\ldots\}$ to be given at times $\{t_0, t_1,\ldots\}$. For $0\leq k$, let the contribution of the k-th drug administration to the quantity of drug in the gut at time t be denoted by $q_{1,k}(t)$ and to the quantity in the serum be denoted by $q_{2,k}(t)$. In view of Eqs. 3 and 4, these are given by

$$q_{1,k}(t) = H(t-t_k)d_k e^{-\alpha_1(t-t_k)} \tag{5}$$

and

$$q_{2,k}(t) = \frac{\alpha_1 H(t-t_k)}{(\alpha_2-\alpha_1)} d_k \left(e^{-\alpha_1(t-t_k)} - e^{-\alpha_2(t-t_k)}\right) \tag{6}$$

where $H(x)$ is a step function defined by

$$H(x) = 1, \text{ for } x \geq 0, H(x) = 0, \text{ for } x < 0. \tag{7}$$

Use of this step function means that formulae 5 and 6 apply for all values of t, including those before t_k, the k-th time in the sequence $\{t_0, t_1,\ldots\}$.

Given the linear nature of the differential Eqs. 1 and 2 and assuming that no drug is present in either the gut or the serum prior to the first scheduled administration, the

quantity of drug in each compartment at time t is the sum of the individual contributions to that compartment from each drug administration. Thus we have

$$Q_1(t) = \sum_{k=0} q_{1,k}(t) = \sum_{k=0} H(t-t_k) d_k e^{-\alpha_1(t-t_k)} \tag{8}$$

and

$$Q_2(t) = \sum_{k=0} q_{2,k}(t) = \frac{\alpha_1}{(\alpha_2-\alpha_1)} \sum_{k=0} H(t-t_k) d_k \times \left(e^{-\alpha_1(t-t_k)} - e^{-\alpha_2(t-t_k)}\right). \tag{9}$$

The serum drug concentration at time t can be derived by dividing Eq. 9 by V, the volume of distribution.

4 A stochastic pharmacokinetic model for a scheduled sequence of drug administrations when omission probabilities are independent

We now explore the effect of non-adherence on the serum drug concentration, noting that this non-adherence can be caused either by the patient failing to take medicines, or by a health care practitioner failing to administer medicine in a hospital or care centre.

Up to this point in the analysis it has been implicit that d_k, the quantity of drug given at the k-th administration, is a deterministic quantity. The key step in our analysis is to revise this assumption and to treat the set of quantities $\{d_k\}$ as independent random variables with expectations $\{E[d_k]\}$ and variances $\{\mathrm{Var}[d_k]\}$ respectively.

Under this revised assumption, at any given time t, the quantities $\{q_{2,k}(t)\}$ are also random variables. However Eq. 9 holds since each term in the series satisfies the differential Eqs. 1 and 2 whether $\{d_k\}$ are random or non-random variables.

Recall that for a set of independent random variables $\{x_k\}$ and a set of constants $\{a_k\}$, the following results apply:

$$E\left[\sum_{k=0} a_k x_k\right] = \sum_{k=0} E[a_k x_k] = \sum_{k=0} a_k E[x_k] \tag{10}$$

and

$$\mathrm{Var}\left[\sum_{k=0} a_k x_k\right] = \sum_{k=0} \mathrm{Var}[a_k x_k] = \sum_{k=0} a_k^2 \mathrm{Var}[x_k]. \tag{11}$$

Applying Eqs. 10 and 11 to 9, the quantity of drug in the serum at time t has an expectation and variance given by:

$$E[Q_2(t)] = \sum_{k=0} E\left[q_{2,k}(t)\right] = \frac{\alpha_1}{(\alpha_2-\alpha_1)} \sum_{k=0} H(t-t_k) \times \left(e^{-\alpha_1(t-t_k)} - e^{-\alpha_2(t-t_k)}\right) E[d_k] \tag{12}$$

and

$$\mathrm{Var}[Q_2(t)] = \sum_{k=0} \mathrm{Var}\left[q_{2,k}(t)\right] = \left(\frac{\alpha_1}{(\alpha_2-\alpha_1)}\right)^2 \sum_{k=0} H(t-t_k) \times \left(e^{-\alpha_1(t-t_k)} - e^{-\alpha_2(t-t_k)}\right)^2 \mathrm{Var}[d_k] \tag{13}$$

$H(x)$ being the step function defined in Eq. 7.

We highlight these equations since they are the key finding in the paper. It should be noted that these results are very general. There are no restrictive assumptions about times at which drug administrations are scheduled and these do not have to be equally spaced. Mathematically, the sequence does not need to be assumed finite.

The nature of the random variables $\{d_0, d_1,\ldots\}$ corresponding to the drug doses taken at times $\{t_0, t_1,\ldots\}$ are also very general. Although they are assumed independent, there are no other implicit assumptions about how they are distributed, other than that the means and variances are defined.

The expressions given in Eqs. 12 and 13 provide a means of calculating the mean and variance of the quantity of drug in the serum, and hence the serum concentration, in a context where the doses of drug received by a patient are not certain. Equivalent results can be obtained pertaining to any additive pharmacokinetic model.

5 A specific case study using the general model

It is useful to illustrate the potential use of the general results summarised in Eqs. 12 and 13 by considering a specific case study (although there are many other scenarios that could be investigated).

5.1 Non-adherence to a regimen of regular drug administrations of equal dose

Here we consider the analysis of a scenario where the intended dose for each scheduled administration is D and

the time interval between each potential administration is I. To model non-adherence we assume that at each scheduled administration there is a fixed probability p that the patient fails to take the drug. We also assume that the patient only takes the drug, if at all, at the scheduled times.

In this context, using standard results from probability theory, the expectation and variance of the amount of drug received at the k-th scheduled administration are given by

$$E[d_k] = D(1-p), \tag{14}$$

and

$$\mathrm{Var}[d_k] = D^2 p(1-p). \tag{15}$$

Setting t_0=0 gives t_k=kI, for $k\geq 0$.

Substituting Eq. 14 into Eq. 12 and Eq. 15 into Eq. 13 gives the following expressions for the expected value and the variance of the serum drug concentration at time t following initiation of treatment, denoted by $\mu(t)$ and $\sigma^2(t)$ respectively:

$$\mu(t) = \frac{D\alpha_1(1-p)}{V(\alpha_2-\alpha_1)} \times \sum_{k=0} H(t-kI)\left(e^{-\alpha_1(t-kI)} - e^{-\alpha_2(t-kI)}\right) \tag{16}$$

and

$$\sigma^2(t) = \left(\frac{D\alpha_1}{(\alpha_2-\alpha_1)V}\right)^2 p(1-p) \times \sum_{k=0} H(t-kI)\left(e^{-\alpha_1(t-kI)} - e^{-\alpha_2(t-kI)}\right)^2. \tag{17}$$

For a given t, these expressions simplify, since there are only a finite number of potential drug administrations that could have occurred by that time. Also, by mathematical good fortune, the series in Eqs. 16 and 17 are geometric progressions and thus re-expressible without summation. Hence, for $n\geq 0$ and $0\leq\tau<I$,

$$\mu(nI+\tau) = \frac{D\alpha_1(1-p)}{V(\alpha_2-\alpha_1)} \times \left[e^{-\alpha_1\tau}\left(\frac{1-e^{-\alpha_1(n+1)I}}{1-e^{-\alpha_1 I}}\right) - e^{-\alpha_2\tau}\left(\frac{1-e^{-\alpha_2(n+1)I}}{1-e^{-\alpha_2 I}}\right)\right] \tag{18}$$

and

$$\sigma^2(nI+\tau) = \left(\frac{D\alpha_1}{V(\alpha_2-\alpha_1)}\right)^2 p(1-p)\times \left[e^{-2\alpha_1\tau}\left(\frac{1-e^{-2\alpha_1(n+1)I}}{1-e^{-2\alpha_1 I}}\right) + e^{-2\alpha_2\tau}\left(\frac{1-e^{-2\alpha_2(n+1)I}}{1-e^{-2\alpha_2 I}}\right) - 2e^{-(\alpha_1+\alpha_2)\tau}\left(\frac{1-e^{-(\alpha_1+\alpha_2)(n+1)I}}{1-e^{-(\alpha_1+\alpha_2)I}}\right)\right] \tag{19}$$

While seemingly complex, these equations are easily evaluated.

5.2 The steady state case in the scenario of equal durations between scheduled drug administrations

This specific example of the application of the general formulae 12 and 13 can be extended.

In the context of the management of a patient with chronic disease where it is intended that a patient follows a specified drug regimen over a long period of time, the mean $\widehat{\mu}(\tau)$ and variance $\widehat{\sigma}^2(\tau)$ of the steady state drug concentration a time τ after a scheduled drug administration can be estimated by taking the limit as n tends to infinity giving, for $0\leq\tau<I$,

$$\widehat{\mu}(\tau) = \frac{D\alpha_1(1-p)}{V(\alpha_2-\alpha_1)}\left(\frac{e^{-\alpha_1\tau}}{1-e^{-\alpha_1 I}} - \frac{e^{-\alpha_2\tau}}{1-e^{-\alpha_2 I}}\right), \tag{20}$$

and

$$\widehat{\sigma}^2(\tau) = \left(\frac{D\alpha_1}{V(\alpha_2-\alpha_1)}\right)^2 p(1-p) \times \left(\frac{e^{-2\alpha_1\tau}}{1-e^{-2\alpha_1 I}} + \frac{e^{-2\alpha_2\tau}}{1-e^{-2\alpha_2 I}} - \frac{2e^{-(\alpha_1+\alpha_2)\tau}}{1-e^{-(\alpha_1+\alpha_2)I}}\right). \tag{21}$$

Having obtained these analytical expressions for the mean and variance of drug concentration at steady state, it is possible to assess the effect of non-adherence on patient care.

From the form of Eq. 6, it can be seen that the random variables $\{q_{2,k}(t)\}$ are not equally distributed. Indeed one may expect that the potential contribution to the serum concentration associated with a recent scheduled administration to be much larger than the potential contribution from a scheduled administration some time ago. In view of this, serum drug concentration at a given point in time cannot be expected to be normally distributed. That said, comparing the mean and standard deviation of the drug concentration to the limits of the therapeutic range provides a strong indication of whether variability in drug concentration due to non-adherence is a cause for clinical concern.

5.3 Numerical consequences in the scenario of equal durations between scheduled drug administrations

The drug mexiletene is used to treat ventricular arrhythmias, especially after myocardial infarction [17]. It can be taken for several months to help prevent arrhythmia, and generally has to be taken three times a day to keep the serum concentration roughly constant. Since arrhythmia is a dangerous condition, patient adherence while taking mexiletene is especially important. The pharmacokinetics of mexiletene can be described by Eqs. 1 and 2 using parameter values available from the literature [18].

Figure 2a and b show the expected serum concentration versus time for the first eight scheduled drug administrations and then the steady state concentrations in the cases where the probability of omitting a scheduled administration is 0.1 and 0.4 respectively. In each case, the bold horizontal line represents the lower limit of the therapeutic range as given in [18].

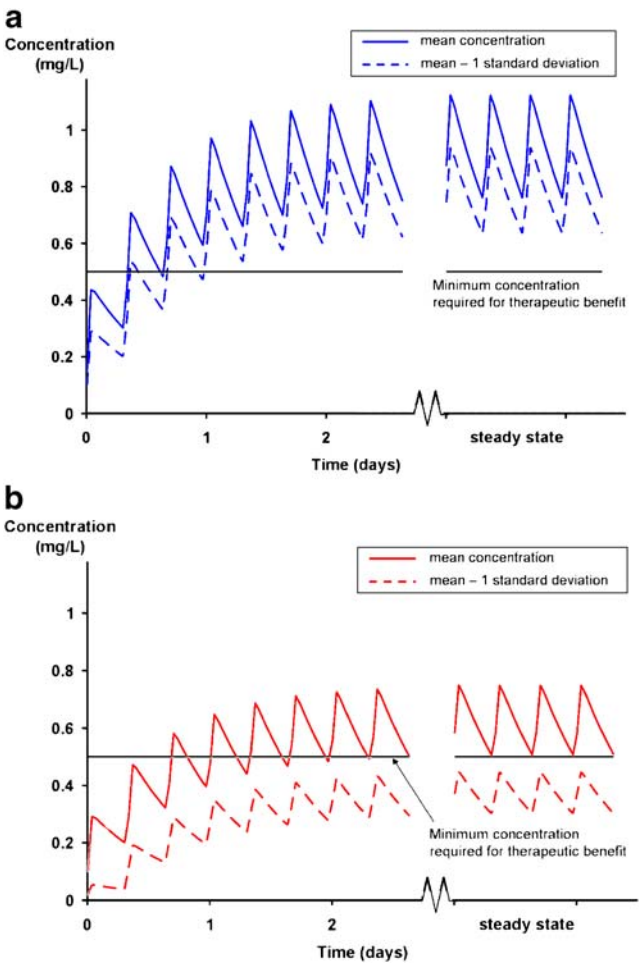

Fig. 2 **a** The serum concentration of mexiletine versus time if the probability of omitting each scheduled dose is 0.1. The *horizontal line* indicates the lower limit of the therapeutic range. **b** The serum concentration of mexiletine vs time if the probability of omitting a scheduled dose is 0.4. The *horizontal line* indicates the lower limit of the therapeutic range

The probability distribution of the serum drug concentration is not Gaussian and using the calculated standard deviation to estimate prediction intervals under the assumption of normality would be misleading. Nonetheless, the standard deviation can give a broad idea of the likely clinical impact of a particular degree of patient non-adherence. If the mean concentration is within the therapeutic range and the standard deviation is only a small fraction of the differences between the mean concentration and each limit of the therapeutic range, then that level of patient non-adherence is probably not a major problem (Fig. 2a). On the other hand, if the standard deviation is the same order of magnitude as the difference between the mean concentration and either limit of the therapeutic range, clearly there would be cause for concern (Fig. 2b).

It would be preferable to have the exact estimates for the probability that a patient with a chronic condition and with a given adherence rate would have a serum drug concentration below the therapeutic range. We have developed an algorithmic method for doing so [19] but giving details of this is beyond the scope of the present paper and is not in keeping with the present theoretical extension of pharmacokinetic theory.

6 Discussion

We have extended deterministic pharmacokinetic modelling to include stochastic features related to the probability that a planned drug administration actually happens. The analysis has considerable generality. For example, both the size of dose and the probability of correct administration may vary for each scheduled administration. Also, our analysis is suitable for assessing both non-adherence on the part of patients and non-adherence to protocol by health care professionals.

The case of a simple absorption and elimination process has been used to illustrate such analysis. In the case where there is a fixed probability of missing a particular drug administration, we have derived explicit formulae for time-varying mean and variance of drug concentrations depending on the drug regimes intended and the rates of adherence, assuming non-adherence errors to be independent of one another.

The approach presented here can be applied to other pharmacokinetic models and hence to a wide range of medicines. In the case of a pharmacokinetic model with more compartments, the relevant equations for the mean and variance of the serum concentration look more complex but are no less tractable. There is also scope for modelling more complex drug regimens involving several drugs

allowing for the possibility that, not only might an administration be missed, but that the wrong drug might be taken. The assumption of the independence of non-adherence errors greatly simplifies our analysis, but alternative models of adherence might also be amenable to similar methods.

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